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Isoniazid for preventing tuberculosis in non-HIV infected persons (Review)

Smieja M, Marchetti C, Cook D, Smaill FM

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[Intervention Review]

Isoniazid for preventing tuberculosis in non-HIV infected persons

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ABSTRACT

Background

Although isoniazid (INH) is commonly used for treating tuberculosis (TB), it is also effective as preventive therapy.

Objectives

The objective of this review was to estimate the effect of six and 12 month courses of INH for preventing TB in HIV-negative people at increased risk of developing active TB.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (May 2003), CENTRAL (*The Cochrane Library* 2003, Issue 2), Science Citation Index (1955 to 1993), Cumulated Index Medicus (1960 to 1970), MEDLINE (1966 to May 2003), EMBASE (1974 to May 2003), and reference lists of articles.

Selection criteria

Randomized controlled trials of INH preventive therapy for six months or more compared with placebo. Follow up for a minimum of two years. Trials enrolling patients with current or previously treated active TB or with known HIV infection were excluded. Criteria were applied by two reviewers independently.

Data collection and analysis

Trial quality was assessed by two reviewers independently, and data extracted by one reviewer using a standardized extraction form.

Main results

Eleven trials involving 73,375 patients were included. Trials were generally of high quality. Treatment with INH resulted in a risk ratio (RR) of developing active TB of 0.40, (95% confidence interval (CI) 0.31 to 0.52), over two years or longer. There was no significant difference between six and 12 month courses (RR 0.44, 95% CI 0.27 to 0.73 for six months, and 0.38, 95% CI 0.28 to 0.50 for 12 months). Preventive therapy reduced deaths from TB, but this effect was not seen for all-cause mortality. INH was associated with hepatotoxicity in 0.36% of people on six months of treatment and in 0.52% of people treated for 12 months.

Authors' conclusions

Isoniazid prevents active TB in diverse at-risk patients, and six- and 12-month regimens have a similar effect. The most recent trial included in the review was published in 1994, and we have not identified any relevant trials up to 2003. We therefore do not plan to update this review.

23 May 2018

No update planned

Research area no longer active

Due to a lack of published data from 1994 onwards, the authors will no longer be updating this review.

PLAIN LANGUAGE SUMMARY

Isoniazid is effective in helping to prevent tuberculosis in people not infected with HIV

Tuberculosis (TB) is a serious bacterial infection and it is estimated that about a third of the world's population is infected with TB. There are a number of types, such as pulmonary TB (bacteria residing in a person's lungs) and spinal TB (in the spine). Some bacteria can be drug resistant and some people may have the infection alongside another medical condition. People suffer from severe cough, weakness and sweats, and some people still die from TB even though effective drug treatment has been around for many years. The incidence of TB has reduced in areas where the drugs are readily available. Preventing people from contracting TB in high-risk areas is a goal worth pursuing. The review of trials using isoniazid for a six- to 12-month period in people without HIV infection (HIV infected people were studied in another review) identified 11 trials involving over 90,000 people. Isoniazid was effective in preventing TB in 60% of people, although some did develop hepatitis. The findings showed that one person can be saved from getting TB when 35 people take isoniazid for six months, and one in every 200 treated will get hepatitis. The balance of benefits and harms need to be carefully considered for each setting where intervention is being considered.

BACKGROUND

Morbidity and mortality from Mycobacterium tuberculosis infection remain high worldwide, with an estimated 8 million active cases and 3 million deaths annually (Kochi 1991). Short course drug therapy, case finding, and directly observed therapy are used widely, whereas preventive therapy with isoniazid (INH) has been used inconsistently in industrialized countries and rarely in developing nations. In recently exposed or high-risk individuals, INH preventive therapy for 6 to 12 months is recommended by:

1. the Joint Tuberculosis Committee of the British Thoracic Society (Joint Tuberculosis Committee of the British Thoracic Society 1994 (JTCBTS 1994); Ormerod 1990);

2. the American Thoracic Society and the Center for Disease Control (American Thoracic Society and the Centers for Disease Control and Prevention 1994 (ATS&CDCP 1994); MMWR 1990);

3. the Canadian Thoracic Society (Standards Committee (Tuberculosis) of the Canadian Thoracic Society and the Canadian Lung Association 1996 (SC(T)CTS&CLA 1996)).

It is also recommended by other groups (American Academy of Pediatrics 1992 (AAP 1992); Barnes 1993; Miller 1993).

Authors of decision and economic analyses have examined the preventive role of INH in various settings (Fitzgerald 1990; Jordan 1991; Rose 1986; Salpeter 1997; Snider 1986, Snider 1988; Stead 1987; Taylor 1981), but estimates used for the effectiveness of INH in these analyses have varied. The purpose of this review was to critically appraise and summarize randomized trials of INH for preventive therapy of TB, and to estimate more precisely the benefits and risks of 6 and 12 month treatment during 2 years or greater of follow-up.

OBJECTIVES

Our primary objective was to estimate precisely the effectiveness of 6 and 12 month courses of INH in the prevention of active pulmonary tuberculosis (TB) in non-HIV populations.

We also assessed INH in preventing extra-pulmonary TB, TB deaths, total mortality, and resistant M. tuberculosis isolates.

METHODS

Criteria for considering studies for this review

Types of studies

Published randomized trials, whether randomised by individual, or cluster (for example, by family, hospital ward, or village).

Types of participants

Populations at risk of developing active tuberculosis, who did not have active TB at study enrolment, were included. HIV-positive studies have been reviewed by Wilkinson (Wilkinson 1998) and were excluded from this review. Studies involving children with primary tuberculosis were excluded, as this would now be considered treatment of disease rather than prophylaxis. Studies of patients with previous tuberculosis were included if the disease was inactive and had not been previously treated with anti-tuberculous chemotherapy.

Types of interventions

Only trials in which isoniazid alone (at least 200 mg daily, or 5 mg/kg) was used for at least 6 months, and compared with placebo, were included.

Types of outcome measures

Primary outcome

Rate of development of active tuberculosis (defined as symptoms, positive microscopy or culture, or change in chest x-ray) over not less than 2 years of follow-up.

Other outcomes

The number of cases of extra-pulmonary tuberculosis, tuberculosis-related and total deaths, hepatotoxicity, other adverse effects, and isolation of isoniazid-resistant Mycobacterium tuberculosis.

Search methods for identification of studies

Relevant studies were identified by computerized searches of the MEDLINE (1966 to May 2003), EMBASE (1974 to May 2003), Cochrane Infectious Diseases Specialized Register (May 2003), and the Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library* (2003, Issue 2, using the terms tuberculosis, isoniazid, prophylaxis, prevention and control, and clinical trials in combinations. The years 1966-2003 were screened. A total of 703 references were obtained, and potentially relevant articles were obtained in full. All references from over 100 articles were scanned for trials of isoniazid preventive therapy.

Many of the reviews and trials were published prior to 1966, and even later ones may not have been appropriately coded in the computer databases. Therefore, an exhaustive search was undertaken of the Science Citation Index (1955-1993) for authors of large trials, (including Ferebee, Comstock, Zorini, Mount, Groth-Peterson), and by subject for 1965-1993 for the key words isoniazid, prevention and control, chemoprophylaxis, and tuberculosis. The Current List of Medical Literature for 1955-1959, and the Cumulated Index Medicus for 1960-1970, were searched under tuberculosis, pulmonary tuberculosis, and isoniazid. Relevant review articles were obtained, and all potential primary articles were obtained in full. Bibliographic references of all obtained reviews and primary articles were examined. English and non-English papers were obtained.

The MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials searches were updated in May 2003, but no new trials were found.

Data collection and analysis

Studies were identified as outlined previously. Fifty-four potentially relevant papers, abstracts, or reviews were identified. From these, studies were selected if they met the following selection criteria:

1. randomized (individual or cluster randomization),
2. use of isoniazid alone versus placebo for 6 months or longer,
3. active tuberculosis at study onset ruled out in participants, and
4. follow-up for development of active tuberculosis over at least 2 years.

Studies were examined independently in duplicate by two of us (MS, CM) with good agreement for inclusion and exclusion in the review (kappa=0.7). There was disagreement on classification of 7 of 54 papers. Differences were resolved by discussion and by re-examination of the relevant studies.

Quality scores were assigned in duplicate to the studies which met the selection criteria. A short checklist of 4 factors made up a validity score out of a possible 10 points, and this was applied to the studies in duplicate. Method of randomization was assigned a maximum of 4 points; degree of blinding, 2 points; methods for verifying active tuberculosis, 2 points; and degree of follow-up, 2 points. In addition, scores were assigned to methods of allocation concealment, generation of allocation sequence, and inclusion of all randomized participants, in accordance with the guidelines of the Cochrane Infectious Diseases Group (Cochrane IDG 1998).

Data was abstracted from the 11 selected studies using a standardized 3-page abstraction sheet. Description of the study, participants, methods of randomization and blinding, follow-up, compliance, and outcome were abstracted. Outcome for 1, 2, 5 and 10 years of follow-up were abstracted, as available.

The estimates of treatment effectiveness from individual trials were examined for homogeneity using the Breslow-Day test.

The summary measure was expressed as a risk ratio, using the Der Simonian and Laird random effects model for estimating 95% confidence intervals. The effectiveness was also expressed as the "numbers needed to treat" (NNT) to prevent a case of active TB, defined as the reciprocal of the absolute risk reduction (Laupacis 1988). Results from the longest available follow-up period of between 2 and 5 years were pooled for all selected studies to estimate the risk ratio of developing active TB associated with use of INH. Five year or longer follow-up was available for 6 studies, between 2 and 5 year follow-up for 4 studies, and 2 year follow-up for 1 study.

RESULTS

Description of studies

Many of the initially identified studies did not meet the inclusion criteria (see 'Characteristics of excluded studies'). The most important reason for exclusion was lack of randomization (Comstock 1972; Debre 1973; Dimond 1968; Dorken 1984; Dormer 1960; Grzybowski 1972; Hsu 1974; Khoury 1969; Mysakowska 1964; Narain 1970; Zorini 1958; Zorini 1961). Other reasons for exclusion were lack of a placebo control (Comstock 1969; Debre 1973; Dimond 1968; Dormer 1959; Dormer 1960; Katz 1962; Katz 1965; Khoury 1969; Mysakowska 1964; Narain 1970; Zorini 1958; Zorini 1961); INH for less than 6 months (Groth-Peterson 1960; Vandiviere 1973); concurrent use of PAS (Clayson 1963; Grzybowski 1972) or ethambutol (Dorken 1984); active primary tuberculosis in children (Ferebee 1957; Lotte 1964; Mount 1961); or follow-up for less than 2 years (Dahlstrom 1960; Nyboe 1963). Four identified studies were of HIV positive populations (Gordin HIV 1997; Hawken HIV 1997; Pape HIV 1993; Whalen HIV 1997) and are not included.

Eleven studies met the selection criteria and are included in this review (see 'Characteristics of included studies').

U.S. Public Health Services Trials (see below)

Four of these studies (Comstock 1962; Ferebee 1962, Ferebee 1963; Mount 1962) were sponsored by the United States Public Health Services. All were started in the 1950s and concluded in the 1960s. Included were large groups of individuals at risk of tuberculosis due to recent or remote contact with an active case of pulmonary tuberculosis; living in geographic areas of high incidence and prevalence of disease; or living in a psychiatric institution. Randomization in these studies was by household, village, or hospital ward. Participants received isoniazid or matching placebo for 1 year, at a dose of 300 mg daily or 5 mg/kg for children. Follow-up was active for 2 years, followed by passive reporting to the public health department for 10 years. Five and 10 year follow-up and long-term toxicities were included in an extensive review (Ferebee 1970).

Comstock, Alaska 1962

This study of 28 villages and 2 boarding schools in Alaska was started in 1958 (Comstock 1962). Initial results were reported in 1962, and subsequently at intervals for 19 years. 7,333 villagers, 95% of whom were Inuit and mostly under the age of 20 years, were randomized by family unit. Infants 2 months of age and older were included. 45% had previous TB exposure, as judged by chest x-ray and skin testing. Follow-up was done by nurses who examined all study participants every 3 months. Follow-up data from this study indicate that the protective effect of INH persists for up to 19 years, although open-label treatment offered to all participants complicates the accurate interpretation of INH versus placebo effectiveness after 10 years. (Comstock 1979). The calculation that 6 months of preventive therapy may be adequate came from the follow-up data in this study, as was the finding that treatment for longer than 12 months does not improve effectiveness.

Mount, US household contacts, 1962

This study of household contacts in the United States (Georgia, South Carolina, Ohio) enrolled families in which a member had previously been diagnosed with active TB (Mount 1962). 3,138 were eligible and 2,824 were examined and enrolled. These were contacts of "known" cases, and exposure had taken place months to years earlier. Children under age 2 months were excluded. 45% had a negative skin test, 60% were black, and 40% white. Previous TB and Epilepsy were excluded. Randomization was by family unit. Compliance was measured by pill count, and 65% took at least 75% of their medication. Follow-up was for four years.

Ferebee, US household contacts, 1962

This study was started in 1957 and enrolled household contacts of newly reported cases of active TB in the United States, Puerto Rico, and Mexico (Ferebee 1962). 47% of study participants were from Puerto Rico. Of 29,087 contacts, 25,033 were enrolled. Randomization was by household. Excluded were cases of previous TB, epilepsy, and infants under age 2 months. 52% were skin test negative. Compliance was assessed by pill counts, with 80% taking at least 75% of their medication. Follow-up was for 10 years. Effectiveness by degree of adherence with medication suggested that participants who took less than 10 months of INH derived considerably less benefit than those taking 10 or more months of INH (Ferebee 1970).

Ferebee, US psychiatric institutions, 1963

This study was started in 1957 and enrolled 37 psychiatric chronic care institutions in the United States (Ferebee 1963). 24,838 patients were randomized by ward (566 wards in total). Patients aged 2 years to over 100 years were included, and 50% had a positive skin test. Mean age was 48 years for men and 54 years for women. 75% took their medication for at least 9 months. Follow-up was for 10 years. This study reported a disproportionate number of deaths in the INH arm (752 versus 611), but analysis of death rates in the year prior to randomization also indicated a similar excess of deaths. The authors attributed this finding to chance (the randomization unit was by ward, and an analysis which treats the total number of patients as individually-randomized will over-estimate the precision of the estimate).

Egsmose, Kenya 1965

This British Medical Research Council study was carried out in rural Kenya, starting in 1959 (Egsmose 1965). 626 household contacts of active TB cases received isoniazid 300-500 mg daily for one to two years. Tuberculosis was measured by sputum positivity. Exclusions were past or present active TB, previous TB, or exposure to the index household fewer than 2 times per week. Allocation was by household. Chest x-rays were done every 3 months during the first year, then twice yearly for one year, then yearly. Compliance was monitored by pill counts and urine testing. Follow-up was for 2 to 4 years.

Del Castillo, Philippines 1965

Del Castillo, at the Quezon Institute in the Philippines, enrolled 400 household contacts of recently diagnosed cases of active pulmonary tuberculosis (Del Castillo 1965). 83% were skin test positive at enrolment. 62% were women. The study was started in 1961. Participants were randomized by family unit to 5-10 mg/kg of INH for one year. Analysis was stratified by tuberculin skin test positivity. X-ray changes were used as the sole criterion for disease, and follow-up was carried out at one and two years. Compliance was not measured. Although the over-all rates of TB were similar in the two arms (16 on INH, 22 on placebo), the protection of INH was greater in those who were initially skin test positive (8 on INH versus 18 on placebo). Follow-up was for 2 years.

Veening, Netherlands 1968

Veening studied 261 of 305 recent skin test converters aged 18-20 years in the Royal Dutch Navy (Veening 1968). The study was started in 1960, with follow-up for 7 years. Participants were treated with 600 mg of INH for 4 months, followed by 400 mg for the next 8 months. Chest x-rays and skin tests were repeated frequently (2 monthly). All participants had known previous negative TB skin tests, and had converted over a 3 month period. A high rate of active TB was seen in the placebo arm (9%), with only a single case in the INH arm (1%), indicative of the early institution of prophylaxis, and the presumed high rate of compliance. Although all participants were individually randomized, the outbreak represented a clonal spread from a single case of active TB.

Falk, U.S. Veterans hospitals 1978

This U.S. Veterans Hospital study was started in 1964, and enrolled men with previous pulmonary tuberculosis (Falk 1978). All had abnormal chest x-rays. Patients were individually randomized. 77% were white, 17% were black. Most were aged 30-50 years, with 16% aged 52-70 years. TB had been inactive for 5-20 years. Those who had been previously treated for tuberculosis were excluded from this analysis. Treatment was with INH for 1-2 years, but only the 1 year arm and placebo are reported in this review. Compliance was 78% with the one year regimen. Chest x-rays were done 6 monthly for 2 years and then yearly. Follow-up was for 5 years. A total of 7,036 were randomized, however only those with no previous TB therapy (2,389) are included in this review. There was an increase in deaths on INH compared with placebo, but these figures did not separate those who had been previously treated with chemotherapy, and are not included in the pooled estimates of total mortality in this review.

Thompson, IUAT Eastern Europe, 1982

This large study of 28,000 Eastern European adults was carried out by the International Union Against Tuberculosis (Thompson 1982). It was started in 1969, and included 115 clinics in Czechoslovakia, Finland, East Germany, Hungary, Poland, Romania, and Yugoslavia. They compared three different lengths of treatment (3, 6 or 12 months) for individuals aged 20-65 years with previous tuberculosis as evidenced by chest x-ray fibrotic changes. Mean age was 50, and all had abnormal tuberculin skin tests (6 mm or greater). Compliance was monitored by reported pill-taking and urine testing. Compliance was measured at 70% for the one year course and 80% for the 6 month course of INH. The 3 month arm is not reported in this review, and had a reduction of 30% in TB cases compared with placebo (not statistically significant). Follow-up was recorded yearly for 5 years, and both tuberculosis and hepatitis were sought. Chest x-rays were obtained yearly. This is the only study with a direct comparison between various lengths of treatment, as well as with prospective ascertainment of rates of hepatitis in both placebo and treated groups.

Girling, Hong Kong, 1992

This British Medical Research Council study was started in 1981 (Girling 1992). 679 Chinese men with pneumoconiosis from silica exposure (silicosis), attending a clinic in Hong Kong, were randomized to INH for 6 months, rifampin for three months, INH and rifampin for 3 months, or placebo. Only the INH and placebo arms are reported in this review. The rates of TB in the INH and rifampin and rifampin alone arms were similar to those taking INH for 6 months. All patients were men, aged 65 years and under, and all had abnormal chest x-rays. They were followed by x-rays and sputum culture for M. tuberculosis over a period of up to 5 years. A very high proportion of those on placebo (34%) developed active TB.

John, India, 1994

In a study of renal transplant and dialysis patients in India, 184 patients were individually randomized to 300 mg INH or placebo for one year (John 1994). Mean age was 34 years, and 16% were women. A high number of drop-outs due to hepatitis (65, equally distributed between INH and placebo arms) occurred in both groups, and a high rate of TB was seen (10%). Patients were treated with INH 300 mg daily for one year. Fewer than 40% were able to comply with the study.

Risk of bias in included studies

Quality assessment included ascertainment of concealed allocation; randomization; blinding; measurement of end-points;

and follow-up. A quality score out of a possible 10 points was assigned in duplicate to the studies which met the selection criteria. Studies were assigned quality scores of 6 to 10, with a median score of 8. Agreement between observers was good (kappa=0.6). The studies which met the selection criteria were of high methodologic quality. No weighting of the results by quality score was done, and all studies are included in the analysis.

Allocation concealment was judged adequate in 6 (random number tables and assignment by pharmacy and off-site); probably adequate in 2; and unknown in 3.

The median quality score was 8 of a possible 10 points. Most of the variation in scores was explained by differences in randomization (units other than the individual). Double-blinding was conducted in all 11 studies. Follow-up of over 80% of the study population was attained in all studies. The diagnosis of TB was made by pre-defined criteria and reviewed by an independent panel in 8 studies. Diagnosis was based on microscopy or culture of sputa, chest x-ray with appropriate symptoms, or a clinical course and response to treatment compatible with TB. A period of five years or longer of follow-up was available for 6 studies, 2 to 5 year follow-up for 4 studies, and 2 year follow-up for 1 study.

Method of randomization was by individual randomization in 5 studies, and by cluster randomization in the remaining 6 studies. Concealment of allocation was difficult to ascertain, but appeared to be good in most studies. Random number tables were used to generate the allocation, and a pharmacist or other person removed from direct patient care supervised the process.

Studies were assessed for single or double-blinding. In all cases, blinding was apparently double-blind, although this was not always stated.

The rigour with which the diagnosis of active tuberculosis was made was assessed. Specifically, a study protocol for the diagnosis of tuberculosis, and a method for independent review of suspected cases, were sought. Nine studies received full scores for these criteria, and a further two satisfied one of these criteria.

Finally, the degree of follow-up was assessed. The percentage of patients followed up at two years (<80%, 80-89%, or >90%) was determined. In nine studies, a full score was assigned for follow-up. All but one used an intention-to-treat analysis, (in which participants are analyzed in the group to which they were randomized, regardless of cross-over or non-compliance), or else did not specify.

Effects of interventions

Fifty-four articles were identified, of which 15 papers describing 11 studies met the inclusion criteria. A dose of 300 mg INH daily, or 5-15 mg/kg for children, for 6-12 months was used in most trials. Six studies were randomized not by individual patients but by families or hospital wards (Comstock 1962; Del Castillo 1965; Egsmose 1965; Ferebee 1962; Ferebee 1963; Mount 1962).

Rates of development of TB varied widely. The baseline risk of TB in patients randomized to placebo in all 11 studies was 557 cases among 33,113 participants, or a rate of 1.7% (range 0.4 to 34.3%) over 5 years. In the U.S. Public Health Services studies of household contacts, institutional residents, and Alaskan villagers, rates of TB in placebo recipients were 0.4 to 5.3%. The highest TB rates occurred in a Hong Kong study of patients with silicosis, in whom one-third developed TB over 5 years (Girling 1992).

In 10 of the 11 studies, INH taken daily for 6 months to 12 months reduced the occurrence of active TB cases over the follow-up period. Amongst a total of 73,375 patients randomized to INH or placebo and followed for the development of active TB, 796 developed disease. Tuberculosis developed in 239 cases randomized to INH and in 557 cases randomized to placebo, for a risk ratio (RR) of 0.40 (95% CI 0.31 to 0.52). No statistically-significant heterogeneity was found (P=0.08). No relationship between quality score and effectiveness was found (r=0.07; P=0.79).

The greatest effectiveness was seen in a Dutch study that followed identification of a remarkable outbreak of TB among Navy personnel (Veening 1968). A single man with open cavitary TB infected 95% of the men in his barracks and 27% of over 1,000 personnel in the compound. In the placebo group, 9.4% developed active TB, whereas only one case was identified among 133 INH recipients. In this study, prophylaxis was instituted rapidly, a high dose of INH was used (600 mg daily initially for 4 months, followed by 400 mg for a total of 1 year), and a high rate of compliance was achieved.

Given a pooled baseline rate of development of TB in the placebo-treated patients of 1.7%, the RR of developing TB of 0.40 in these patients receiving INH confers an absolute risk reduction of 0.01. Therefore 100 individuals would need therapy to prevent one case of active TB over the subsequent 5 years (NNT=100).

The relative effectiveness of 6 and 12 month regimens of INH were compared both directly and indirectly. The only direct (within-study) comparison of 6 versus 12 month courses of INH preventive therapy was in the IUAT study (Krebs 1976; Thompson 1982), in which TB developed in 34 of 6,965 (0.49%) patients allocated to 6 months INH, versus 24 of 6919 (0.35%) allocated to 12 months, for a RR of 1.41 (95% CI 0.84 to 2.37). In a sub-group analysis of highly compliant participants completing 6 or 12 month regimens, TB developed in 0.5% of those taking 6 months of INH and in 0.1% in those taking 12 months of INH (Thompson 1982). Indirect (between-study) comparison of 6 versus 12 month INH preventive therapy was made by pooling all 10 studies in which 12 month regimens were used, (RR: 0.38, 95% CI 0.28 to 0.50) and comparing this result with the pooled RR from 2 studies using 6 month regimens (RR: 0.44, 95% CI 0.27 to 0.73).

Most studies reported total cases of TB, and actively sought only cases of pulmonary TB. In 4 studies, 37 cases of extra-pulmonary TB, among 44,636 patients randomized, were reported (Ferebee 1962; Ferebee 1963; Girling 1992; Mount 1962). Nine of 22,379 (0.04%) randomized to INH, and 28 of 22,257 (0.13 %) randomized to placebo, developed extra-pulmonary TB, for a RR of 0.34 (95% CI 0.16 to 0.71).

Cause-specific mortality was reported in 2 studies, with 3 deaths (0.12%) attributed to TB among patients randomized to INH, and 10 TB deaths (0.29%) in the placebo arms, giving a RR of 0.29 (95% CI 0.07 to 1.18). Total mortality was reported in 5 studies (Comstock 1962; Egsmose 1965; Ferebee 1963; John 1994; Mount 1962), with 1,573 deaths among 33,716 participants. The pooled RR is 1.10 (95% CI 0.94 to 1.28), suggesting no effect of INH on total mortality.

Side effects of INH were reported infrequently, and included mild and transient headache, nausea, and dizziness. The most serious adverse effect of hepatotoxicity was prospectively assessed and comprehensively reported in the International Union Against Tuberculosis (IUAT) study (Thompson 1982), in which patients took 0, 3, 6 or 12 month regimens of INH. A placebo rate of hepatitis of 0.12% was observed in the first year. Rates of hepatitis for 3, 6 and 12 month courses of INH were 0.25%, 0.36%, and 0.52% respectively. A total of 95 patients of 20,840 receiving INH developed hepatitis, and 3 died. However, no monitoring of serum liver enzymes or discontinuation of medication for biochemical or clinical signs of hepatotoxicity was done in this study.

In the 5 studies that sought and reported M. tuberculosis resistance, 9 isolates from 137 patients (6.6%) taking placebo were INH resistant, compared with 13 isolates from 63 patients (20.6%) taking INH (Ferebee 1970). As Ferebee noted in her review (Ferebee 1970), the absolute number (9 versus 13) rather than the per cent of isolates is more relevant, since INH-resistant isolates would not be prevented by INH therapy. From these data, there appears to be no increase in the number of INH-resistant isolates following INH preventive therapy.

DISCUSSION

Tuberculosis continues to be a major global threat to human health. This review was conducted to generate the most current, valid estimate of the effectiveness of isoniazid in preventing active tuberculosis. We critically appraised and summarized the results of 4 decades of randomized controlled trial evidence, and found a clinically important and statistically significant benefit of INH preventive therapy. The risk ratio of 0.40 (95% CI 0.31 to 0.52) in non-HIV populations is consistent with the range of risk ratios in the individual U.S. Public Health Service trials (95% CI 0.17 to 0.41) reported in 1970 by Ferebee (Ferebee 1970).

Wilkinson, in a Cochrane Collaboration review of HIV-positive populations, found the effectiveness of any preventive therapy regimen (INH, INH plus rifampin, or INH plus rifampin plus pyrazinamide) to be associated with an odds ratio (OR) of 0.52 (95% CI 0.36 to 0.76) (Wilkinson 1998). INH effectiveness was demonstrated in the skin-test positive sub-group (OR=0.37), and was similar to our pooled RR of 0.40 for INH effectiveness in the HIV-negative population.

The Joint Tuberculosis Committee of the British Thoracic Society and the American Thoracic Society and the Centers for Disease Control and Prevention recommend preventive therapy for a minimum of 6 months in patients at increased risk of developing TB, such as recent skin test converters, close contacts of known TB cases, or patients with positive skin tests with chronic medical conditions (JTCBTS 1990; JTCBTS 1994; ATS&CDCP 1994). The ATS&CDC guidelines recommend 12 months of INH for skin-test positive, HIV-positive patients. Our review confirms the effectiveness of INH in diverse populations, and demonstrates a small advantage of 12 over 6 month courses of INH preventive therapy. This small advantage of 12 over 6 month courses may not be worthwhile except for those at high risk of developing TB.

The advantage of longer courses of INH was greater in the one study which had a direct randomized comparison of 12 versus 6 months, but the estimate was not statistically significant. This advantage appeared even greater if only those highly compliant with INH were compared. However, this was a non-randomized sub-group analysis, and if non-compliance is a marker for tuberculosis risk, it may have over-estimated INH effectiveness. Nevertheless, high compliance was associated with increased effectiveness, and recently the American Thoracic Society and Centers for Disease Control and Prevention re-examined these trials and concluded that the optimal period for INH preventive therapy may be 9 months (O'Brien 1998).

The Joint Tuberculosis Committee recommends 6 months of INH preventive therapy for children exposed to M. tuberculosis (Ormerod 1990), whereas the American Academy of Pediatrics recommends 9 months of therapy (AAP 1992). In this review, children were included in 6 of the 12 month trials, but no children were enrolled in the 6 month studies. No randomized trials were identified which examined a 9 month duration of preventive therapy. Thus, the adequacy of 6 and 9 month regimens in the paediatric population requires confirmation. Three children died of accidental INH overdoses (Comstock 1962; Ferebee 1962), underlying another potential risk in the paediatric population.

The primary risk of preventive therapy is the risk of INH-induced hepatitis. In the IUAT study, 1 person in 200 developed hepatitis, and 1 person in 7,000 died from INH-induced hepatitis (Thompson 1982). Kopanoff, in a US Public Health Service cooperative surveillance study of 13,838 people taking INH preventive therapy, found 92 probable and 82 possible cases of hepatitis, with 8 fatalities (Kopanoff 1978; Snider 1992). Age over 35 years, and daily alcohol ingestion, were significantly associated with higher rates of hepatitis. In a meta-analysis of INH-associated mortality, Salpeter found only 2 INH-associated deaths among 200,000 patients treated since 1982 (Salpeter 1993), and concluded that the true rate of attributable fatalities is very low with appropriate selection and monitoring of patients.

How might clinicians apply these findings to individual patients? We propose assessing patients for preventive therapy based on estimates of the numbers needed to treat (McQuay 1997). Such an estimate requires an accurate baseline assessment of TB risk, an estimate of the benefit of treatment (RR of 0.40 for INH over all; 0.38 for 12 months and 0.44 for 6 months), and an estimate of harm (0.005 incidence of INH hepatitis for average patient, higher as age increases over 35 years). Conversion of benefit into NNT and harm into "number needed to harm" (NNH) may allow a more informed decision to be made by clinicians and their patients.

Consider a remotely-exposed asymptomatic adult with a positive skin test and a normal chest x-ray, with a 1% risk of developing active TB over 5 years. From the IUAT study, the risk of hepatitis is less than 0.5%, or a NNH of 200 (Thompson 1982). A six-month course is associated with an NNT of 179, that is, approximately 179 such individuals require therapy to prevent one case of active TB over 5 years. Conversely, a 12-month course is associated with an NNT of 161, but the incremental benefit of 12 over 6 months is small, and an additional 1667 patients require treatment for the second 6 months to prevent a case of TB not prevented by the first 6 months. (Note that a lower NNT is obtained if one uses the point estimates from the IUAT trial of 6 and 12 month efficacy). Such an incremental NNT may or may not be acceptable to clinicians or patients, and preventive therapy of low risk individuals might not be offered, or limited to 6 months when it is offered.
The recent household contact with a skin-test conversion has approximately a 5% risk of developing active TB over 5 years of

follow-up, (and another 5% lifetime risk). In this population, the NNT for 6 months is 36, and 32 for 12 months. This compares favorably with other preventive strategies in medicine, and should be considered together with the risk of harm and the patient's preferences. The benefit of 12 over 6 months is marginal: an additional 333 patients would require therapy to prevent a further case of TB.

In high-risk individuals, however, the difference in effectiveness between 6 and 12 month regimens may be clinically important. Consider the skin test positive patient with silicosis and a 20% (or higher) baseline risk of developing active TB. For every 9 patients treated for 6 months and for every 8 patients treated for 12 months, one case of active TB will be prevented. The incremental benefit is less for the second six months of preventive therapy: for every 83 patients treated for the additional 6 months, one additional case of TB will be prevented. Clinicians and patients may be willing to accept this benefit.

Several caveats are in order. First, INH is not 100% effective. After exposure to INH-sensitive M. tuberculosis, some cases of TB will occur despite preventive therapy, and INH will not prevent TB caused by exposure to INH-resistant strains of M. tuberculosis. Second, our estimates from trials with moderate compliance may under-estimate the effectiveness achieved in highly compliant individuals. Third, the results of 5 years of follow-up may not predict long-term TB risk. However, a 30-year follow-up of a cohort of children suggests that treatment benefit is likely to be life-long (Hsu 1984).

This review of published randomized trials confirms the effectiveness of isoniazid in preventing the development of active TB in a wide variety of at-risk groups. Family contacts, skin test converters, institutional residents, patients with chronic renal or respiratory conditions, adults with healed pulmonary TB on x-ray, and villagers in endemic areas, benefited from INH preventive therapy. These estimates of effectiveness of INH preventive therapy may be useful for incorporation into future economic evaluations and decision analyses. Moreover, the estimates of the numbers needed to treat may help clinicians and patients decide whether to initiate preventive therapy, and for how long. Ultimately, decisions about duration of preventive therapy are made by patients and clinicians, considering issues of potential benefit and harm, adherence to medication, convenience, and patient preferences.

AUTHORS' CONCLUSIONS

Implications for practice

This review re-affirms the effectiveness of INH in preventing the development of active tuberculosis in approximately 60% of individuals in various at-risk groups. Family contacts, skin test converters, institutional residents, patients with chronic renal disease or silicosis, and villagers in endemic areas, were shown to benefit from INH preventive therapy. In most studies, a dose of 300 mg daily, or 5-15 mg/kg, was used for 6-12 months.

These findings support the current recommendations of using INH for preventive therapy in risk groups such as household contacts, recent skin-test converters, individuals with chronic renal or respiratory disease at high risk of TB reactivation, and patients with healed tuberculosis on chest x-ray.

For the recent household contact with a positive tuberculin skin test, for every 35 patients prescribed INH for 6 months, the clinician will be preventing one case of active tuberculosis over the next 5 years. However, one of every 200 patients given prophylaxis will develop INH-induced hepatitis. In patients at low baseline risk, INH may be effective but hundreds of patients would require prophylaxis to prevent a case of tuberculosis. In these patients, risk likely out-weights the benefit. Conversely, at high risk, the incremental benefit of 12 months over 6 months of prophylaxis may be worthwhile. Estimates of baseline risk, efficacy, and harm, expressed as the numbers needed to treat, may allow clinicians to tailor decisions to individual patients more effectively than existing guidelines. Decisions about duration of preventive therapy are made by patients and clinicians, considering issues of potential benefit and harm, adherence to medication, convenience, and patient preferences.

Implications for research

This review provides a summary of the literature and a pooled estimate of effectiveness of INH for preventive therapy of tuberculosis. The pooled estimates for active tuberculosis, extra-pulmonary tuberculosis, total mortality, and rates of hepatitis provide the best current estimates from clinical trials. Several areas have been identified for future research.

First, overall effectiveness was a risk ratio of 0.40, or a risk ratio reduction of 60%. Effectiveness was greater in highly compliant study participants, but these estimates were non-randomized sub-group analyses and may over-estimate INH effectiveness. An effectiveness of 60% risk reduction may be acceptable in low to medium risk populations, but is sub-optimal for those at high risk. The development of more effective regimens for those at high risk are required.

Second, although a 12 month course of INH is slightly more effective than a 6 month course, this difference is not statistically significant and may not be clinically relevant except for those at high risk. Authors of guidelines and public health recommendations need to be more explicit in defining the numbers of individuals whom they would be willing to treat to prevent a case of tuberculosis. There may be vast differences in this threshold for preventive therapy between individual clinicians, patients and public health officials, and these need to be explored.

Third, optimal duration of preventive therapy in children remains undetermined. No children were included in the trials of 6 months duration, and thus randomized trial data is available only for 12 month duration. Yet, effectiveness of 6 months is likely to be similarly effective.

Fourth, decision analyses have often considered reduction of mortality as a goal of INH prophylaxis, yet such a reduction in all-cause mortality could not be demonstrated in this review. Further research is required to ascertain whether INH prophylaxis yields any reduction in all-cause mortality.

The most recent trial included in the review was published in 1994, and we have not identified any relevant trials up to 2003. We therefore do not plan to update this review.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Comstock 1962

Methods	Randomization by family unit.
Participants	7,333 Alaskan villagers in 28 villages and 2 boarding schools. Enrolled regardless of PPD status.
Interventions	Isoniazid 300 mg daily for 1 year.
Outcomes	1. Active tuberculosis
Notes	—

Del Castillo 1965

Methods	Randomization by family unit.
Participants	400 household contacts of index cases treated at Quezon Institute, Manila, Phillippines.
Interventions	Isoniazid 5-10 mg/kg for 1 year.
Outcomes	1. Active tuberculosis
Notes	—

Egsmose 1965

Methods	Randomization by household. Allocation by random numbers tables.
Participants	626 Kenyan rural villagers, contacts of index cases.
Interventions	Isoniazid 300-500 mg daily for 12-24 months.
Outcomes	1. Pulmonary tuberculosis (sputum microscopy or culture) 2. Deaths
Notes	—

Falk 1978

Methods	Individual randomization.
Participants	7,036 men in U.S. VA hospitals; abnormal chest x-ray. 98% men; mostly 30-50 years old. 77% white.
Interventions	Isoniazid 300 mg daily 1-2 years.
Outcomes	1. Active tuberculosis
Notes	Majority of this group had received previous TB medications and were excluded from analysis. 2,389 participants included.

Ferebee 1962

Methods	Randomization by family unit.
Participants	25,033 household contacts of newly diagnosed reported tuberculosis. 2/3 under 20 years old.
Interventions	Isoniazid 300 mg/kg or 5 mg/kg for one year.
Outcomes	1. Active tuberculosis 2. Extrapulmonary tuberculosis 3. Death
Notes	—

Ferebee 1963

Methods	Randomization by ward or building.
Participants	24,838 patients in 37 county institutions for chronic psychiatric or mentally retarded in Wisconsin, Georgia, and Massachusetts, U.S.A. PPD >5mm in 50%. Age 2-100, >85% white, mean age 48 (men) 54 (women).

Ferebee 1963 *(Continued)*

Interventions	Isoniazid 300 mg daily for 12 months.
Outcomes	1. Active tuberculosis 2. Death
Notes	91% had normal chest x-ray, 9% abnormal at baseline.

Girling 1992

Methods	Inidividual randomization.
Participants	679 Chinese men with silicosis in Hong Kong. Most 45-64, 63% current smokers, 94% >10mm. Criteria: silicosis diagnosis, no history TB, no evidence TB, negative sputum microscopy and culture.
Interventions	INH 300 mg daily 6 months; Rifampin 600 mg daily 12 weeks; INH + Rif 12 weeks; placebo.
Outcomes	1. Active tuberculosis
Notes	All had abnormal chest x-rays. Only the INH and placebo arms included in this review (total 199).

John 1994

Methods	Individual randomization, random numbers table.
Participants	184 transplant or dialysis patients in India.
Interventions	Isoniazid 300 mg or placebo for one year. Low compliance.
Outcomes	1. Active tuberculosis 2. Hepatitis 3. Death
Notes	High rates of drop out and hepatitis in both groups.

Mount 1962

Methods	Randomization by family unit.
Participants	2,824 household contacts of known tuberculosis cases (prevalent cases) in USA. 1/3 children; 55% PPD< 5mm; 60% black.
Interventions	Isoniazid 300 mg daily for one year.
Outcomes	1. Active tuberculosis 2. Extrapulmonary tuberculosis

Mount 1962 *(Continued)*

	3. Deaths
Notes	—

Thompson 1982

Methods	Individual randomization.
Participants	28,000 adults in Eastern Europe: 115 clinics Czechoslovakia, Finland, German Democratic Republic, Hungary, Poland, Romania, Yugoslavia. Mean age 50 (20-65), attending chest clinic, abnormal chest x-ray, no previous treatment, no previous positive bacteriology. 1/3 were age 55-65. PPD>6mm.
Interventions	Isoniazid for 3, 6 or 12 months or placebo.
Outcomes	1. Active tuberculosis 2. Hepatitis
Notes	Only placebo, 6 and 12 month arms included in this analysis (total of 20,828).

Veening 1968

Methods	Individual randomization.
Participants	261 PPD positive contacts of active cases in Royal Netherlands Navy barracks.
Interventions	Isoniazid 600 mg for 4 months then 400 mg daily for total 1 years.
Outcomes	1. Active tuberculosis
Notes	Close follow-up and attention to compliance.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bush 1961	Only 1 year follow-up results. At one year: 5/1096 INH treated versus 6/1048 placebo treated original interpretation 8 vs 11. US PHS reinterpreted.
Chiba 1963	Included PAS with INH.
Clayson 1963	Co-intervention with PAS.

Study	Reason for exclusion
Comstock 1969	No placebo group.
Comstock 1972	No randomization.
Curry 1967	Non-randomized.
Dahlstrom 1960	No clinical end-point, follow-up less than 2 years.
Debre 1973	No placebo group, no randomization.
Dimond 1968	No placebo control, no randomization.
Dorken 1984	No randomization, co-intervention with ethambutol.
Dormer 1959	No randomization.
Dormer 1960	No randomization, no placebo.
Ferebee 1957	Primary tuberculosis in children.
Gordin HIV 1997	HIV positive population.
Groth-Peterson 1960	Inadequate dose: 400 mg twice weekly for two thirteen week periods. Follow-up numbers do not match original reports.
Grzybowski 1972	No randomization, concurrent use of PAS.
Hawken HIV 1997	HIV positive population.
Hsu 1974	Non-randomized.
Katz 1962	Non-random allocation, no use of placebo.
Katz 1965	Non-random allocation, no use of placebo.
Khoury 1969	No placebo group, no randomization.
Lotte 1964	Primary tuberculosis in children.
Mount 1961	Primary tuberculosis in children.
Mysakowska 1964	No placebo group, no randomization.
Narain 1970	No randomization, no placebo.
Nyboe 1963	One-year follow-up only, never published.
Pamra 1971	Incomplete follow-up and unclear measure of active tuberculosis.
Pape HIV 1993	HIV positive population.
Vandiviere 1973	INH and BCG co-interventions; INH for less than 6 months.
Whalen HIV 1997	HIV positive population.

Study	Reason for exclusion
Zorini 1958	Non-randomized, no placebo.
Zorini 1961	Non-randomized, no placebo.
Zorini 1963	Non-randomized, no placebo.

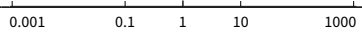
DATA AND ANALYSES

Comparison 1. Isoniazid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active tuberculosis	11	73375	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.31, 0.52]
2 Extra-pulmonary tuberculosis	4	44636	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.16, 0.71]
3 TB deaths	2	25714	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.07, 1.18]
4 Hepatitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Hepatitis-related deaths	2	25714	Risk Ratio (M-H, Random, 95% CI)	4.13 [0.50, 34.39]
6 Total deaths	5	33716	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.94, 1.28]

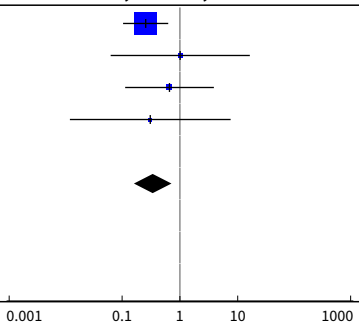
Analysis 1.1. Comparison 1 Isoniazid versus placebo, Outcome 1 Active tuberculosis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Comstock 1962	50/2480	128/2406		15.79%	0.38[0.27,0.52]
Del Castillo 1965	16/126	22/167		9.63%	0.96[0.53,1.76]
Egsmose 1965	7/325	18/301		6.13%	0.36[0.15,0.85]
Falk 1978	5/889	15/772		4.84%	0.29[0.11,0.79]
Ferebee 1962	8/8478	36/8311		7.18%	0.22[0.1,0.47]
Ferebee 1963	61/12339	173/12499		16.58%	0.36[0.27,0.48]
Girling 1992	20/100	34/99		12.07%	0.58[0.36,0.94]
John 1994	7/92	10/92		5.53%	0.7[0.28,1.76]
Mount 1962	6/1462	12/1348		5.07%	0.46[0.17,1.22]
Thompson 1982	58/13838	97/6990		15.74%	0.3[0.22,0.42]
Veening 1968	1/133	12/128		1.44%	0.08[0.01,0.61]
Total (95% CI)	**40262**	**33113**		**100%**	**0.4[0.31,0.52]**
Total events: 239 (Treatment), 557 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=20.94, df=10(P=0.02); I^2=52.26%					
Test for overall effect: Z=7.06(P<0.0001)					



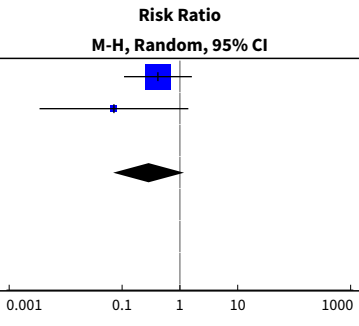
Analysis 1.2. Comparison 1 Isoniazid versus placebo, Outcome 2 Extra-pulmonary tuberculosis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ferebee 1962	6/8478	23/8311		69.36%	0.26[0.1,0.63]
Ferebee 1963	1/12339	1/12499		7.28%	1.01[0.06,16.19]
Girling 1992	2/100	3/99		17.9%	0.66[0.11,3.87]
Mount 1962	0/1462	1/1348		5.46%	0.31[0.01,7.54]
Total (95% CI)	**22379**	**22257**		**100%**	**0.34[0.16,0.71]**
Total events: 9 (Treatment), 28 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.54, df=3(P=0.67); I^2=0%					
Test for overall effect: Z=2.84(P=0)					



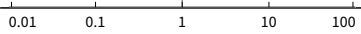
Analysis 1.3. Comparison 1 Isoniazid versus placebo, Outcome 3 TB deaths.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Comstock 1962	3/2480	7/2406		78.92%	0.42[0.11,1.61]
Thompson 1982	0/13838	3/6990		21.08%	0.07[0,1.4]
Total (95% CI)	**16318**	**9396**		**100%**	**0.29[0.07,1.18]**
Total events: 3 (Treatment), 10 (Control)					
Heterogeneity: Tau^2=0.18; Chi^2=1.13, df=1(P=0.29); I^2=11.77%					
Test for overall effect: Z=1.73(P=0.08)					



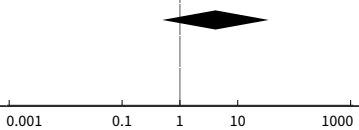
Analysis 1.4. Comparison 1 Isoniazid versus placebo, Outcome 4 Hepatitis.

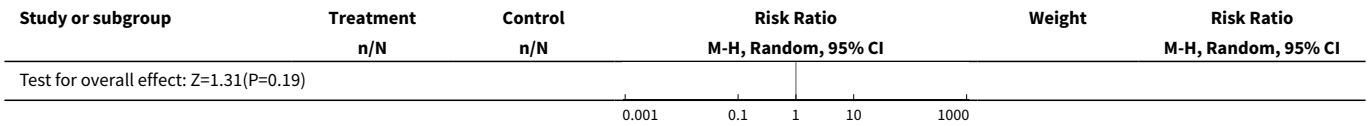
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Thompson 1982	77/13884	7/6990		5.54[2.56,12]



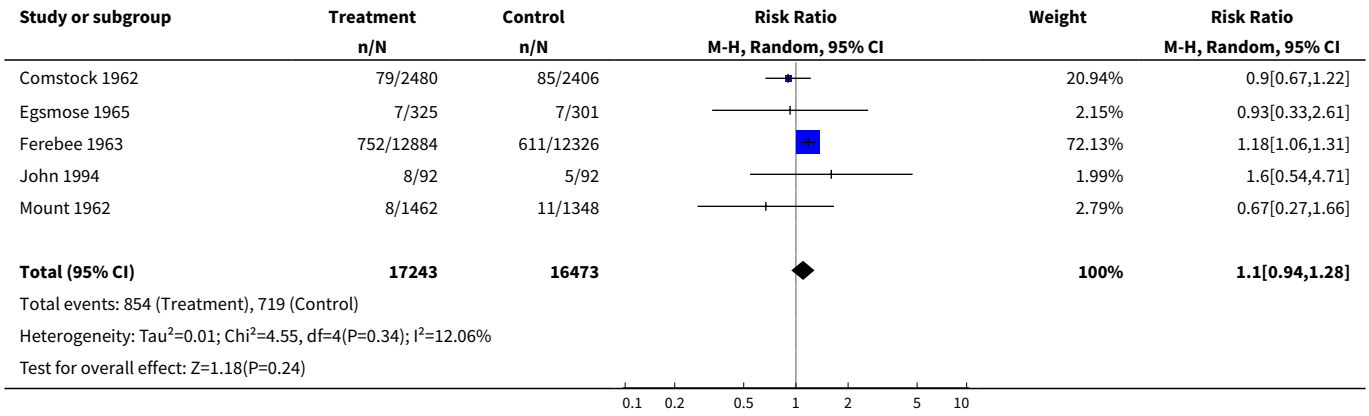
Analysis 1.5. Comparison 1 Isoniazid versus placebo, Outcome 5 Hepatitis-related deaths.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Comstock 1962	2/2480	0/2406		48.79%	4.85[0.23,100.99]
Thompson 1982	3/13838	0/6990		51.21%	3.54[0.18,68.45]
Total (95% CI)	**16318**	**9396**		**100%**	**4.13[0.5,34.39]**
Total events: 5 (Treatment), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					





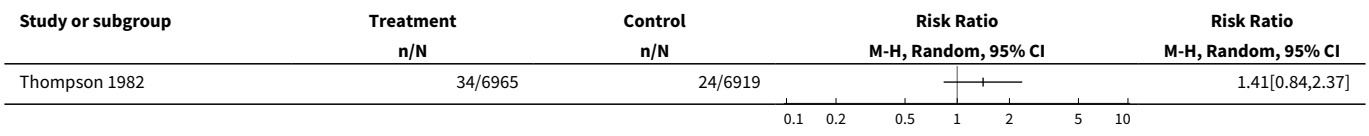
Analysis 1.6. Comparison 1 Isoniazid versus placebo, Outcome 6 Total deaths.



Comparison 2. Isoniazid 6 vs 12 months

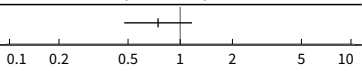
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active tuberculosis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Hepatitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Active tuberculosis in highly compliant	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Isoniazid 6 vs 12 months, Outcome 1 Active tuberculosis.



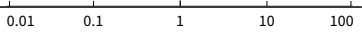
Analysis 2.2. Comparison 2 Isoniazid 6 vs 12 months, Outcome 2 Hepatitis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Thompson 1982	33/6965	44/6919		0.75[0.48,1.17]



Analysis 2.3. Comparison 2 Isoniazid 6 vs 12 months, Outcome 3 Active tuberculosis in highly compliant.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Thompson 1982	25/5437	5/4543		4.18[1.6,10.9]

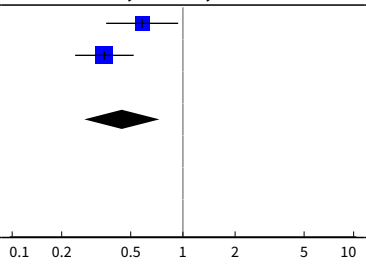


Comparison 3. INH 6 months vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active tuberculosis	2	14145	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.27, 0.73]

Analysis 3.1. Comparison 3 INH 6 months vs placebo, Outcome 1 Active tuberculosis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Girling 1992	20/100	34/99		46.19%	0.58[0.36,0.94]
Thompson 1982	34/6956	97/6990		53.81%	0.35[0.24,0.52]
Total (95% CI)	**7056**	**7089**		**100%**	**0.44[0.27,0.73]**
Total events: 54 (Treatment), 131 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=2.64, df=1(P=0.1); I^2=62.11%					
Test for overall effect: Z=3.19(P=0)					

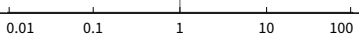


Comparison 4. INH 12 months+ vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active tuberculosis	10	66257	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.28, 0.50]

Analysis 4.1. Comparison 4 INH 12 months+ vs placebo, Outcome 1 Active tuberculosis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Comstock 1962	50/2480	128/2406		17.78%	0.38[0.27,0.52]
Del Castillo 1965	16/126	22/167		11.48%	0.96[0.53,1.76]
Egsmose 1965	7/325	18/301		7.56%	0.36[0.15,0.85]
Falk 1978	5/889	15/772		6.04%	0.29[0.11,0.79]
Ferebee 1962	8/8478	36/8311		8.77%	0.22[0.1,0.47]
Ferebee 1963	61/12339	173/12499		18.53%	0.36[0.27,0.48]
John 1994	7/92	10/92		6.87%	0.7[0.28,1.76]
Mount 1962	6/1462	12/1348		6.32%	0.46[0.17,1.22]
Thompson 1982	24/6919	97/6990		14.79%	0.25[0.16,0.39]
Veening 1968	1/133	12/128		1.87%	0.08[0.01,0.61]
Total (95% CI)	**33243**	**33014**		**100%**	**0.38[0.28,0.5]**
Total events: 185 (Treatment), 523 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=19.29, df=9(P=0.02); I^2=53.34%					
Test for overall effect: Z=6.64(P<0.0001)					

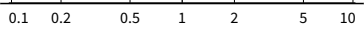


Comparison 5. High compliance (>80%) INH vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active tuberculosis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 High compliance (>80%) INH vs placebo, Outcome 1 Active tuberculosis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Thompson 1982	30/10080	83/5616		0.2[0.13,0.31]



WHAT'S NEW

Date	Event	Description
10 November 2009	Review declared as stable	Due to a lack of published data from 1994 onwards, the authors will no longer be updating this review. This decision was taken in August 2006, prior to the introduction of a formal Cochrane policy, hence the necessity to republish now as 'no longer updated'.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 1, 1999

Date	Event	Description
21 July 2008	Amended	Converted to new review format with minor editing.
15 August 2006	Amended	2006, Issue 4 (minor update): Synopsis added along with text in the abstract and review conclusions to notify readers that the review will not be updated in future.
6 May 2003	New search has been performed	New studies sought but none found

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development, UK.
- European Commission (Directorate General XII), Belgium.

INDEX TERMS

Medical Subject Headings (MeSH)

*HIV Infections; Antitubercular Agents [*therapeutic use]; Isoniazid [*therapeutic use]; Tuberculosis, Pulmonary [*drug therapy]

MeSH check words

Humans